10-551106

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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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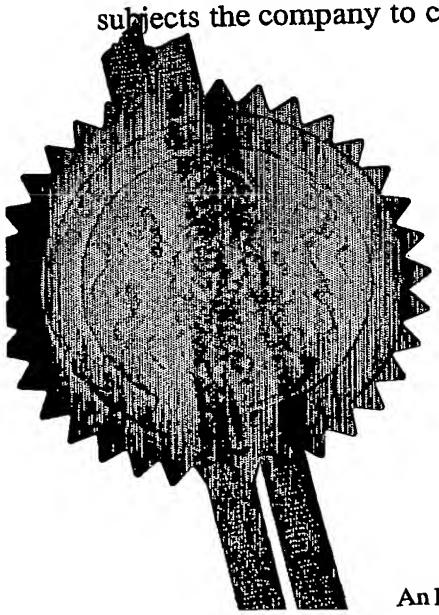

Signed Gleph Hardy.

Dated 30 January 2004

PGM/EP2004 7 0032 55

**Patents Form 1/77**

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31MAR03 E794282-1 000528
P01/7700 0.00-0307277.4

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## Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

| | | |
|---|---|---|
| 1. | Your reference | G-33005P1/BCK 9936 |
| 2. | Patent application number *(The Patent Office will fill in this part)* | 0307277.4 |
| 3. | Full name, address and postcode of the or of each applicant *(underline all surnames)* | BIOCHEMIE GESELLSCHAFT MBH<br>A-6250 KUNDL, TIROL<br>AUSTRIA 83551 58001 |
| | Patent ADP number *(if you know it)* | |
| | If the applicant is a corporate body, give the country/state of its incorporation | AUSTRIA |
| 4. | Title of invention | Organic compounds |
| 5. | Name of your agent *(If you have one)*<br>"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* | Novartis Pharmaceuticals<br>UK Limited<br>Patents and Trademarks<br>Wimblehurst Road<br>Horsham West Sussex<br>RH12 5AB |
| | Patents ADP number *(if you know it)* | 7181522002 |

| | | Country | Priority application number *(if you know it)* | Date of filing (day/month/year) |
|---|---|---|---|---|
| 6. | If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number | | | |

| | | Number of earlier application | Date of filing (day/month/year) |
|---|---|---|---|
| 7. | If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application | | |

| | | |
|---|---|---|
| 8. | Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*<br>*a) any applicant named in part 3 is not an inventor, or*<br>*b) there is an inventor who is not named as an applicant, or*<br>*c) any named applicant is a corporate body.*<br>*(see note (d))* | Yes |

## Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

| | |
|---|---|
| Continuation sheets of this form | |
| Description | 7 |
| Claim(s) | 3 |
| Abstract | |
| Drawing(s) | |

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | |
| Request for substantive examination *(Patents Form 10/77)* | |
| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co.

Date: 28th March 2003

**B.A. Yorke & Co.**

12. Name and daytime telephone number of person to contact in the United Kingdom

**Mrs S Schnerr**
**020 8560 5847**

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*After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.*

### Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

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**Organic Compounds**

This invention relates to pharmaceutical compositions of venlafaxine.

Venlafaxine is the non-proprietary name for 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and is useful in treating a number of disorders including depression, anxiety, panic disorder and pain. Venlafaxine is administered as venlafaxine hydrochloride in treating depression. See The Merck Index, 12th Edition, entry 10079.

Published European patent application EP 797 991 A discloses encapsulated extended release formulations of venlafaxine hydrochloride which comprise a hard gelatin capsule containing spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and hydroxypropylmethylcellulose coated with ethyl cellulose and hydroxypropylmethylcellulose. Solvents used in the coating step include methylene chloride and anhydrous methanol.

The present applicants have sought to overcome the drawbacks of hitherto known formulations of venlafaxine.

In one aspect, therefore, this invention provides coated core pellets comprising venlafaxine for use in a delayed release formulation which core pellets undergo at least one coating step in the absence or substantial absence of organic solvents.

In another aspect, this invention provides a coated pellet comprising

a) a pellet core which comprises venlafaxine hydrochloride;

b) a first coating which comprises a lipophilic layer or a sparingly water-soluble layer, and

c) a second coating which comprises a water-soluble polymer.

The pellet core may comprise in addition a carrier, for example microcrystalline cellulose. The pellet core may comprise in addition a binder, for example a cellulose derivative, e.g. hydroxypropylmethylcellulose (HPMC). The present applicants have found that HPMC of e.g. grade K 4 M has an appropriate viscosity for use in this invention.

The pellet core may be spheroidal in geometry and typically exhibits a diameter, when coated, of between around 0.5 mm to 2 mm, e.g. 0.8 mm to 1.5 mm.

The first coating and second coating may each be complete or substantially complete, e.g. so as to provide a surface coverage of at least 60 %, e.g. 70 % or more, e.g. 80 to 95 % around the core (first coating) or around the first coating (second coating). Complete coatings are preferred.

The first coating serves to protect the pellet core from moisture, both in storage and in use.

The lipophilic layer may comprise a fat, fatty alcohol or wax. The lipophilic layer preferably comprises cetostearyl alcohol, castor oil or dibutyl phthalate.

The sparingly water-soluble layer may comprise a sugar, e.g. lactose, in the form of an aqueous suspension wherein the concentration of the sugar is at least about 0.1 g/ml, e.g. 0.15 to 0.25 g/ml or greater, e.g. 0.28 g/ml to 0.4 g/ml or even higher.

The water-soluble polymer may be selected from acrylate-based aqueous dispersions and ethylcellulose aqueous dispersions.

In a preferred aspect, the pellet core and/or coating(s) of this invention are free of, or substantially free of, polyvinylpyrrolidone.

In another aspect, this invention provides a composition comprising coated pellets as herein described. The composition may be in tablet, hard gelatine capsule or sachet form.

In another aspect, this invention provides a coated pellet consisting of or consisting essentially of

a) a core containing venlafaxine hydrochloride in an amount of between 30 and 60 % by weight, microcrystalline cellulose in an amount of between 40 and 65% by weight, and HPMC K 4 M in an amount of between 0.3 and 0.8% by weight, wherein the respective weights are in relation to the double-coated core;

b) a first coating containing cetostearyl alcohol in an amount of between 1.7 and 3.5 % by weight of the first-coated pellet core; and

c) a second coating containing an acrylate-based polymer in an amount of between 9 and 13 % by weight based on the total weight of the double-coated core, and talc in an amount of between 3 and 8 % by weight based on the total weight of the double-coated pellet core.

Suitable acrylate-based polymers are available commercially e.g. from the Röhm company, Germany, under the trade marks EUDRAGIT or SURELEASE, e.g. EUDRAGIT NE 30 D, EUDRAGIT RL 30 D, EUDRAGIT RS 30 D or KOLLCOAT SR as dry polymer.

The second coating may further comprise triethyl citrate or dibutyl phthalate, e.g. in an amount of 10 to 30 % by weight of the dry polymer.

In a further aspect, this invention provides a composition consisting of or consisting essentially of coated pellets as herein described. The composition may be in tablet, hard gelatine capsule or sachet form.

In a further aspect, this invention provides a process for preparing pellets as herein described which comprises the steps of

i) forming a pellet core mixture comprising venlafaxine hydrochloride with water or an aqueous solution of a binder,

ii) extruding and spheronising the mixture, and subsequently drying,

iii) applying the first coating,

iv) applying the second coating, and subsequently sieving so as to obtain coated pellets within the desired size range,

wherein the process is carried out in the absence or substantial absence of any organic solvent at least in the second layer.

Coating steps iii) and iv) may employ conventional fluidised bed processes. Alternatively, the first coating layer may be applied using a spray melt process.

In another embodiment, the first coating layer may be dissolved in an organic solvent medium, e.g. methylene chloride or methanol, and sprayed onto the pellet cores.

A preferred embodiment of the above process is such that the process is carried out in the absence or substantial absence of any organic solvent in both the first coating layer and in the second coating layer.

The venlafaxine hydrochloride is sourced from the Medichem company, India. The venlafaxine may be used in any polymorphic form, e.g. in the forms known as Form I or Form II.

The compositions of this invention may be administered to adults in doses ranging from 75 mg to 350 mg venlafaxine per day.

Following is a description by way of example only of compositions of this invention.

Example 1

Pellets according to the following composition are prepared and filled into hard gelatin capsules.

| | | Quantity per capsule (mg) |
|---|---|---|
| I | Core pellets | |
| | venlafaxine HCl | 169.70 |
| | microcrystalline cellulose | 199.0 |
| | HPMC K 4 M | 1.85 |
| II | Wax coating | |
| | cetostearyl alcohol | 9.26 |
| III | Polymer coating | |
| | Eudragit NE 30 D | 56.97 |
| | talc | 28.49 |
| | Total weight of coated pellets | 476.90 |

The core pellets are prepared by mixing the above components with a small amount of water, i.e. enough to form a paste without dissolving the venlafaxine, under I followed by extrusion spheronisation. The wax coating is applied using a fluidised bed process at or close to the melting temperature of the coating layer. The subsequent polymer (sustained release) coat is applied by a fluidised bed process. The resulting coated pellets are sieved so as to obtain a desired pellet size range of between 0.85 mm and 1.75 mm.

Example 2

Pellets are prepared in analogous manner to those in Example 1 with replacement of the wax coating by an aqueous suspension of lactose at a concentration of 0.15 g/ml. The suspension is sprayed onto the cores using a perforated pan or a fluidised bed process.

In view of the small amount of water involved in the first coating step, negligible dissolution of venlafaxine takes place and a protective layer is formed between the pellet core and the second coating.

Example 3

A capsule composition is prepared in analogous manner to that in Example 1 with the following component amounts.

| | | |
|---|---|---|
| I | Core pellets | Quantity in % |
| | venlafaxine HCl | 37.3 % by weight of core pellets |
| | microcrystalline cellulose | 62.1 % by weight of core pellets |
| | HPMC K 4 M | 0.5 % by weight of core pellets |
| II | Wax coating | |
| | cetostearyl alcohol | 2.5 % by weight of core pellets |
| III | Polymer coating | |
| | Eudragit NE 30 D (dry) | 15% by weight of pellets with first coating |
| | talc | 50% by weight of dry polymer |

The following dissolution profiles are observed using USP Apparatus 1 at 100 rpm in purified water at 37°C.

| Time (hours) | Cumulative amount dissolved (%) EFFEXOR ER | Formulation of Example 3 | Dissolution range in FOI* (%) |
|---|---|---|---|
| 2 | 14 | 8 | < 30 |
| 4 | 40 | 32 | 30 to 55 |
| 8 | 67 | 68 | 56 to 80 |
| 12 | 79 | 85 | 65 to 90 |
| 24 | 93 | 98 | > 80 |

* FOI is understood to mean Freedom of Information in this context.

The principal advantages of the pellets and compositions of the present invention include a release profile of venlafaxine as effective as the commercially available product, however without the use of an organic solvent medium at least for application of the second coating. A further advantage is the absence of any organic solvent residue in the coated pellets. The coated pellets of this invention are thus produced using more environmentally attractive processes than hitherto known processes for venlafaxine.

Claims

1. A coated pellet comprising

a) a pellet core which comprises venlafaxine hydrochloride;

b) a first coating which comprises a lipophilic layer or a sparingly water-soluble layer, and

c) a second coating which comprises a water-soluble polymer.

2. A pellet as claimed in claim 1 wherein the core additionally comprises a carrier, e.g. microcrystalline cellulose.

3. A pellet as claimed in claim 1 or claim 2 wherein the core further comprises a binder.

4. A pellet as claimed in claim 3 wherein the binder comprises a cellulose derivative

5. A pellet as claimed in claim 3 or claim 4 wherein the binder comprises hydroxypropyl methylcellulose.

6. A pellet as claimed in claim 1 or claim 2 wherein the lipophilic layer comprises a fat, fatty alcohol or wax.

7. A pellet as claimed in any preceding claim wherein the lipophilic layer comprises cetostearyl alcohol, castor oil or dibutyl phthalate.

8. A pellet as claimed in claim 1 or claim 2 wherein the sparingly water-soluble layer comprises a sugar, e.g. lactose, in the form of an aqueous suspension wherein the concentration of the sugar is at least ?? mg/ml.

9. A pellet as claimed in any preceding claim wherein the water-soluble polymer is selected from polymethacrylate dispersions and ethylcellulose dispersions.

10. A composition comprising pellets as claimed in any preceding claim.

11. A composition as claimed in claim 10 in tablet, hard gelatine capsule or sachet form.

12. A process for preparing coated pellet cores which process comprises the steps of

i) forming a pellet core mixture comprising venlafaxine hydrochloride with water or an aqueous solution of a binder,

ii) extruding and spheronising the mixture, and subsequently drying,

iii) applying a first coating,

iv) applying a second coating, and subsequently sieving,

wherein the process is carried out in the absence or substantial absence of any organic solvent medium at least in the second coating.

13. A process as claimed in claim 12 wherein the process is carried out in the absence or substantial absence of any organic solvent medium in both the first and second coatings.

14. A pellet, composition or process substantially as herein described with particular reference to the Examples.